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CASE REPORT

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Infantile Refsum disease associated with hypobetalipoproteinemia

Muneaki Matsuo[1*], Tsugio Akutsu[2], Naomi Kanazawa[2] and Nobuyuki Shimozawa[3]

[1]Department of Pediatrics, Saga University, Faculty of Medicine, Saga, Japan

[2]Department of Neurology, Kitasato University, School of Medicine, Kanagawa, Japan

[3]Division of Genomics Research, Life Science Research Center, Gifu University, Gifu, Japan

Abstract

Infantile Refsum disease (IRD) is a rare peroxisome biogenesis disorder with wide range of clinical severity. Herein, we report a mild form of IRD who had been followed as a symptomatic hypobetalipoproteinemia resembling with abetalipoproteinemia. At 6 year-of-age, the patient was diagnosed as having hypobetalipoproteinemia with spinocerebellar degeneration, peripheral neuropathy, retinitis pigmentosa, mild mental retardation, and sensorineural hearing loss. Although low vitamin E levels normalized after oral supplementation, the patient's clinical symptoms worsened very slowly. At 30 years of age, elevated levels of very long chain fatty acids and phytanic acid and decreased plasmalogen levels were detected in the plasma. Genetic analysis revealed a homozygous mutation of Q67R in PEX10. Although hypocholesterolemia is relatively common in IRD, it has been overlooked so far. Since there are many similarities between IRD and abetalipoproteinemia or symptomatic hypobetalipoproteinemia, care should be taken to differentiate symptomatic hypobetalipoproteinemia from IRD.

Keywords: *infantile Refsum disease, peroxisome, hypobetalipoproteinemia*

Introduction

Infantile Refsum disease (IRD) is the mildest phenotype of peroxisome biogenesis disorder, which is also called Zellweger spectrum. It exhibits a variety of clinical manifestations, with wide ranging severity, including psychomotor retardation, dysmorphism, hypotonia, seizures, ataxia, retinitis pigmentosa, and sensorineural hearing loss [1,2].

Previously we reported a variant form of hypobetalipoproteinemia associated with ataxia, hearing loss and retinitis pigmentosa resembling with abetalipoproteinemia [3]. However, recently, the patient was diagnosed with IRD.

Case Report

The patient is 31-year-old man. His parents were second cousins. Development during infancy was normal: the patient could walk alone, but unsteadily, from 17 months of age. However, he could not speak until 2 years of age, when hearing impairment was noted. Growth was within normal limits. The patient had no history of persistent diarrhea or loose stool suggesting fat malabsorption. At 6 years of age, he visited our hospital because of unsteady gait. His IQ was 70, and his speech was slightly slurred. Ophthalmological examination revealed retinitis pigmentosa and hyperopia. He had mild bilateral hearing loss which did not affect ordinary conversation. There was mild proximal muscle weakness and reduced tone. Muscle atrophy was not present. Deep tendon reflexes were absent. Plantar responses were flexor. The gait was ataxic. Romberg's sign was positive. Bilateral coordination movements were impaired. Sensation was normal except for a diminished sense of vibration. The laboratory examination revealed hypolipidemia as shown in Table 1. He was diagnosed as having hypobetalipoproteinemia with spinocerebellar degeneration mimicking abetalipoproteinemia. Although low vitamin E levels normalized after oral supplementation, the patient's clinical symptoms worsened very slowly. The patient has been using a wheelchair since high school. Magnetic resonance imaging showed slowly progressive cerebellar atrophy. Marked lymphedema of the legs developed in the second decade. At 30 years of age, elevated levels of very long chain fatty acids and phytanic acid and decreased plasmalogen levels were detected in the plasma (Table 2).

Total-Cholesterol (mg/dl)	61	
HDL- Cholesterol (mg/dl)	24	
LDL- Cholesterol (mg/dl)	43	
Triglyceride (mg/dl)	60	
Phospholipids (mg/dl)	77	
ApoA1 (mg/dl)	80	(119-155)
ApoA2 (mg/dl)	18	(26-36)
ApoB (mg/dl)	31	(73-109)
ApoC2 (mg/dl)	0.5	(1.8-4.6)
ApoC3 (mg/dl)	1.2	(5.8-10)
Bile acids (μmol/L)	13	<10
Vitamin A (U/L)	1070	(650-2760)
Vitamin E (μmol/L)	0.93	(1.74-3.27)

Table 1. *Patien's lipid and lipoprotein levels.*

		Average	SD
C24:0/C22:0	1.46	1.05	0.16
C25:0/C22.0	0.067	0.024	0.006
C26:0/C22:0	0.109	0.012	0.005
Plasmalogen	0.016	(0.020-0.029)	
Phytanic acid	0.0259	0.0009	0.0008
DHA	0.191	(0.086-0.297)	

Table 2. *Fatty acid analysis*

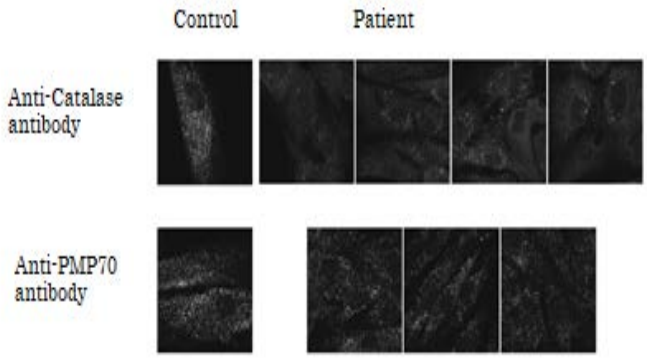

Figure 1. *Immunofluorescence examination of patient's fibroblast.*

After the informed consent was taken from his parents, the patient was examined about peroxisomal disorder according to the study approved by the Ethical Committee of the Graduate School of Medicine, Gifu University. Immunofluorescence examination of patient's fibroblast using rabbit antibodies for human catalase and 70 kDa peroxisomal membrane protein (PMP70) revealed decreased catalase positive particles and normal PMP staining, suggesting impaired peroxisomal matrix protein import with intact PMP biogenesis (Figure 1). Genetic analysis revealed a homozygous mutation of Q67R in PEX10. Q67 in the PEX10 occurred at evolutionally conserved amino acids, and PROVEAN, Polyphen2, and Mutation Taster predicted that the Q67R would be damaging to the protein features, supporting pathogenicity of the mutation. Concerning the rest 11 pathogenic genes of Zellweger spectrum, no mutation was detected in any coding regions of the complete cDNA for PEX2, 3, 5, 13, 14, 16 and 26, nor in any coding regions or exon-intron junctions of the PEX1, 6, 12 and 19 genes. The patient's parents had heterozygous mutations of the PEX10 gene.

Discussion and conclusion

Hypocholesterolemia and low HDL-cholesterol are relatively common in IRD [2,4]. Furthermore, low LDL- cholesterol and triglyceride levels are sometimes reported in IRD [5]. This abnormal lipid metabolism partly accounts for the lipid malabsorption due to abnormal bile acid metabolism associated with IRD; however, these lipid abnormalities persist after the neonatal period, when patients show symptoms of malabsorption. No malabsorption symptoms were evident in the present case.

Although the underlying mechanism is unclear, lipoprotein abnormalities have been reported in IRD [5]. Abnormally increased bile acids in IRD can interact with the G-protein-coupled bile acid receptor TGR5 and nuclear receptors such as the farnesoid X receptor (FXR), resulting in decreased hepatic lipogenesis and decreased triglycerides [6]. Decreased plasmalogen in IRD can also affect cholesterol trafficking [7].

Clinically, there are many similarities between IRD and abetalipoproteinemia or symptomatic hypobetalipoproteinemia, such as retinal degeneration, ataxia, and low cholesterol and vitamin E levels. Care should be taken to differentiate symptomatic hypobetalipoproteinemia from IRD.

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Correspondence: Muneaki Matsuo, Department of Pediatrics, Saga University, Faculty of Medicine, Saga, Japan, Tel: +81-952-34-2314, Fax: +81-952-34-2064; E-mail: matsuo@cc.saga-u.ac.jp

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